

# The Checkpoint Immunotherapy Revolution

## What Started as a Trickle Has Become a Flood, Despite Some Daunting Adverse Effects; New Drugs, Indications, and Combinations Continue to Emerge

Walter Alexander

In June 2010, a long and frustrating drought ended when clinical trial results for ipilimumab (Yervoy, Bristol-Myers Squibb) in metastatic melanoma were presented at the annual meeting of the American Society of Clinical Oncology (ASCO). The drought—comprising the failure of about 70 randomized trials over 30 years to show improved outcomes in melanoma—was relieved by a significant survival advantage for the new monoclonal antibody targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a gene that limits the ability of T cells to attack cancer cells.

The trial involved 676 patients with stage III or IV metastatic melanoma. Lead investigator Steven O'Day, MD, of the Angeles Clinic and Research Institute in Santa Monica, California, reported a median overall survival (OS) of 10.1 months for ipilimumab monotherapy compared with 6.4 months for the experimental glycoprotein 100 (gp100) peptide vaccine (hazard ratio, 0.68;  $P = 0.0004$ ). One- and two-year survival rates with ipilimumab, 46% and 24%, were nearly double the 25% and 14% with the gp100 vaccine, which was chosen as the control because dacarbazine, despite frequent use, had never been proven superior to best supportive care in a randomized trial. Adding the gp100 vaccine to ipilimumab for some patients offered no advantage over ipilimumab monotherapy.<sup>1</sup>

### A Breakthrough With Concerns

Ipilimumab's breakthrough benefits arrived in the company of considerable safety and tolerability concerns. Immune-related adverse events were reported in approximately 60% of patients receiving ipilimumab compared with about 30% of those receiving only gp100. Common autoimmune-related side effects associated with ipilimumab included fatigue, diarrhea, skin rash, endocrine deficiencies, and colitis. Severe or fatal autoimmune reactions were reported in 12.9% of ipilimumab patients. When severe side effects occurred, doctors stopped ipilimumab and administered corticosteroids, but not all patients responded to this treatment. Some patients who *did* respond saw no improvement for several weeks.

The Food and Drug Administration (FDA) announced ipilimumab's approval for treatment of unresectable or metastatic melanoma in March 2011.<sup>2</sup> While this was the agency's first approval for a checkpoint blockade drug—and the only one it would issue for almost 3½ years—it would not be the last. New drugs, new combinations, and new indications began to emerge quickly by late 2014.

One of those recent approvals expanded ipilimumab's labeling to include adjuvant therapy in patients with stage III melanoma for lowering the

risk of disease recurrence after surgery.<sup>3</sup> This approval, added in October 2015, was based on a 951-patient study comparing ipilimumab to placebo as adjuvant therapy following complete surgical removal of melanoma lesions.<sup>4</sup> Recurrence-free survival (RFS) was the primary endpoint (Table 1). Side effects led to treatment discontinuation in nearly half of the ipilimumab patients, mostly within three months. Rates for diarrhea of any grade were 41.4% with ipilimumab and 16.7% with placebo (grade 3 in 9.6% and 0.4%, respectively). Colitis rates were 15.9% and 1.3%, respectively, and grade 3 to 4 in 7.6% and 0.2%. While no deaths were reported in the placebo arm, five (1.1%) were reported in the ipilimumab arm: three from colitis (two with gastrointestinal perforation) and one each from myocarditis and Guillain-Barré syndrome. Rates of endocrine disorders (hypophysitis and hypothyroidism) were elevated in the ipilimumab arm at 37.6% versus 6.5% in the placebo arm.

Although most immune-related adverse events resolved within six weeks, endocrine effects took a median of 31 weeks and resolved in only 56% of patients. A separate study (by Ryder et al.) of endocrine-related adverse events following ipilimumab use in 256 advanced melanoma patients treated in clinical trials between 2007 and 2013 revealed an 8% incidence of hypophysitis.<sup>5</sup> While hormone replacement successfully treated symptoms, endogenous hormone secretion rarely recovered. And the reported hypophysitis rate of 8%, Ryder and colleagues observed, is probably an underrepresentation because clinical presentation is often nonspecific and indistinguishable from the constitutional symptoms of cancer. Also, they wrote, "inadequate anterior pituitary hormone evaluations and the presence of exogenous steroids ... may mask the symptoms and biochemistries" of occult or subclinical hypophysitis. In at least a fourth of the patients with hypophysitis in this analysis, pituitary MRIs were normal.

### The Anti-PD-1 Agents Arrive

The ipilimumab strategy of counteracting immune-cell disempowerment by inhibiting checkpoints is also used in the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. "They allow the immune system to reacti-

**Table 1 RFS Per Independent Review in EORTC 18071<sup>4</sup>**

	Ipilimumab (n = 475)	Placebo (n = 476)	HR, Ipilimumab Vs. Placebo	P Value
Median RFS in months	26.1 (19.3–39.3)	17.1 (13.4–21.6)		
Three-year RFS in months	46.5% (41.5–51.3)	34.8% (30.1–39.5)	0.75 (0.64–0.90)	0.0013

EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; RFS = recurrence-free survival.

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vate against the tumor,” said Roy S. Herbst, MD, PhD, Yale School of Medicine Professor of Pharmacology and Chief of Medical Oncology. While PD-1 is on the immune cell, PD-L1 is on the tumor cell. “When the two are able to interact with each other, that turns off the immune system. So we are trying to block that PD-1 and PD-L1 lock-and-key interaction.”

The first approval for a checkpoint inhibitor was followed, after a pause of more than three years, by a remarkable flurry of announcements and approvals. In early September 2014, Merck announced that at the European Society of Medical Oncology meeting in Madrid it would present data on treatment of multiple advanced solid tumor types (bladder, gastric, melanoma, renal cell carcinoma, non-small-cell lung cancer [NSCLC], and head and neck cancer) with its anti-PD-1 antibody pembrolizumab (Keytruda). Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.<sup>6</sup> Two days later the FDA granted accelerated approval to Keytruda for treatment of advanced or unresectable melanoma.<sup>7</sup>

Pembrolizumab had been granted breakthrough therapy, priority review, and orphan drug status. It was the first agent blocking the PD-1 cellular pathway to secure U.S. approval. In binding to the PD-1 receptor and blocking the interaction with PD-L1 and PD-L2, pembrolizumab evokes an antitumor immune response by releasing PD-1 pathway-mediated inhibition. Patients are eligible to receive pembrolizumab after they have been treated with ipilimumab, and, if their tumors express the *BRAF* V600 mutation, after treatment with a *BRAF* inhibitor as well.

In a test of pembrolizumab at either 2 mg/kg (n = 89) or 10 mg/kg (n = 84) every three weeks among 173 patients,<sup>8</sup> the overall response rate in both groups was 26% after a median follow-up of eight months. Safety profiles were similar as well in the two groups, with no treatment-related deaths. The only drug-related grade 3 or 4 adverse event seen in more than one patient was grade 3 fatigue (3%) in the 2 mg/kg group. The more common drug-related adverse events in the 2-mg/kg and 10-mg/kg groups, respectively, were fatigue (33% versus 37%), pruritus (26% versus 19%), and rash (18% versus 18%).

In the safety analysis, pneumonitis occurred in 12 of 411 patients (2.9%), including grade 2 and 3 in eight (1.9%) and one (0.2%) patients, respectively. Colitis (including microscopic colitis) occurred in four patients (1%), including grade 2 and 3 in one (0.2%) and two (0.5%) patients, respectively. Hypophysitis was reported in 0.5% of patients, nephritis in 0.7%, and hypothyroidism and hyperthyroidism in 8.3% and 1.2%, respectively.

The recommended dose of pembrolizumab is 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks.<sup>9</sup>

### Nivolumab Reaches the Market

In November 2014, a phase 3 study (CheckMate-066) of nivolumab (Opdivo), Bristol-Myers Squibb's investigational programmed cell death immune checkpoint inhibitor entry, demonstrated a survival benefit compared with dacarbazine chemotherapy for treatment-naïve *BRAF* wild-type advanced

melanoma. One-year survival rates were 73% for nivolumab and 42% for dacarbazine, representing a 58% reduction in the risk of death in the nivolumab group ( $P < 0.0001$ ).<sup>10</sup>

In early December 2014, results of the phase 1b CheckMate-039 study of nivolumab in 23 patients with relapsed or refractory Hodgkin lymphoma were presented at the American Society of Hematology meeting and published simultaneously online in the *New England Journal of Medicine*.<sup>11</sup> They showed an overall response rate of 87%, with four patients (17%) achieving a complete response and 16 patients (70%) a partial response. When responses occurred, they took place within eight weeks in 60% of those cases (range, three to 39 weeks). Progression-free survival (PFS) at 24 weeks was 86%. The most severe adverse events were grade 3 myelodysplastic syndrome and pancreatitis, reported in five patients (22%).

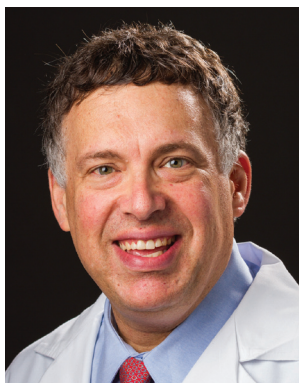
On December 22, 2014, the FDA approved nivolumab for advanced melanoma.<sup>12</sup> In March 2015, the agency added treatment of advanced squamous NSCLC to nivolumab's indications, based on a gain of 3.2 months in OS compared with docetaxel among 272 patients.<sup>13</sup>

Half a year further along, the approval floodgates opened wider, starting with the approval of the nivolumab/ipilimumab combination for *BRAF* V600 wild-type melanoma on September 30, 2015,<sup>14</sup> then the approval of pembrolizumab for advanced NSCLC on October 2, 2015,<sup>15</sup> and the approval of nivolumab, also in NSCLC, on October 9, 2015.<sup>16</sup> With hardly a pause, the

FDA approved nivolumab for treatment of metastatic renal cell carcinoma in November, based on a 5.4-month extension of OS (25 months versus 19.6 months) compared with everolimus (Afinitor, Novartis) in an 821-patient study. Complete or partial responses were observed in 21.5% of the nivolumab group versus 3.9% with everolimus.<sup>17</sup>

A month later, the pembrolizumab indication for advanced melanoma was extended to first-line treatment, based on phase 3 KEYNOTE-006 findings showing 37% and 31% reductions in risk of death for two dosing regimens (100 mg/kg every two weeks or every three weeks) compared with ipilimumab ( $P < 0.001$ ;  $P = 0.004$ ). Grade 3 to 4 treatment-related adverse events occurred in 13.3% and 10.1% of the two-week and three-week pembrolizumab groups and for 19.9% in the ipilimumab group. The treatment-related discontinuation rates for those three groups were 4.0%, 6.9%, and 9.4%, respectively. One treatment-related death occurred in the ipilimumab group. Grade 3 to 4 colitis and hypophysitis rates for ipilimumab were 7.0% and 1.6%, respectively. For the two-week and three-week groups, colitis rates were 1.4% and 2.5%, and the hypophysitis rate was 0.2%. Grade 3 to 4 hepatitis was reported at rates of 1.1% and 1.8% for the pembrolizumab two-week and three-week groups.<sup>18</sup>

Approvals continue in 2016. In January, the FDA granted accelerated approval to nivolumab in combination with ipilimumab for the treatment of patients with *BRAF* V600 wild-type and *BRAF* V600 mutation-positive unresectable or metastatic melanoma based on PFS in the CheckMate-067 trial.<sup>19</sup> FDA-approved immunotherapies are listed in Table 2.



Roy S. Herbst, MD, PhD

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**Table 2 FDA-Approved Immunotherapies**

Agent	Mechanism of Action	FDA Approval Dates and Indications <sup>2,3,7,12–19</sup>
Ipilimumab (Yervoy, Bristol-Myers Squibb)	mAb targeting CTLA-4	<ul style="list-style-type: none"> <li>March 25, 2011: unresectable or metastatic melanoma</li> <li>September 30, 2015: <i>BRAF</i> V600 wild-type unresectable or metastatic melanoma (in combination with nivolumab)</li> <li>October 28, 2015: adjuvant therapy to lower recurrence risk of stage III melanoma after surgery</li> </ul>
Pembrolizumab (Keytruda, Merck)	mAb targeting PD-1	<ul style="list-style-type: none"> <li>September 4, 2014: advanced or unresectable melanoma</li> <li>October 2, 2015: metastatic NSCLC with tumors that express PD-L1 and disease progression on or after platinum-containing chemotherapy</li> <li>December 18, 2015: First-line treatment of unresectable or metastatic melanoma</li> </ul>
Nivolumab (Opdivo, Bristol-Myers Squibb)	mAb targeting PD-1	<ul style="list-style-type: none"> <li>December 22, 2014: unresectable or metastatic melanoma that has progressed following ipilimumab and, if <i>BRAF</i> V600 mutation positive, a <i>BRAF</i> inhibitor</li> <li>March 4, 2015: metastatic squamous NSCLC with progression on or after platinum-based chemotherapy</li> <li>September 30, 2015: <i>BRAF</i> V600 wild-type unresectable or metastatic melanoma (in combination with ipilimumab)</li> <li>October 9, 2015: metastatic NSCLC that has progressed during or after platinum-based chemotherapy</li> <li>November 23, 2015: metastatic renal cell carcinoma after prior anti-angiogenic therapy</li> <li>January 23, 2016: <i>BRAF</i> V600 wild-type and <i>BRAF</i> V600 mutation-positive unresectable/metastatic melanoma (in combination with ipilimumab)</li> </ul>
Talimogene laherparepvec (Imlygic, Amgen)	Oncolytic virus therapy	<ul style="list-style-type: none"> <li>October 27, 2015: local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery</li> </ul>

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; mAb = monoclonal antibody; NSCLC = non–small-cell lung cancer; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

## Researchers and Clinicians Weigh In

How are these approvals affecting treatment? Jeffrey S. Weber, MD, PhD, who recently joined the NYU Langone Medical Center faculty as Deputy Director of the Perlmutter Cancer Center and Co-Director of its Melanoma Program, has been at the forefront of research into how novel agents (e.g., anti-CTLA-4 and anti-PD-1) boost cancer immunity by inhibiting checkpoint molecules on T cells. “Many [patients] will still get single-agent PD-1 inhibitors up front,” he said in an interview. Clinical trials are being conducted to investigate combinations of anti-PD-1 agents and another drug, he said, usually to discourage regulatory T cells (Tregs) or myeloid-derived suppressor cells (MDSCs) from proliferating. “Many patients with aggressive, bulky disease will be receiving ipilimumab plus nivolumab,” he said.

Dr. Weber explained that the smaller fraction of patients with fast-growing, high-lactate dehydrogenase melanoma who are *BRAF* wild-type will get the ipilimumab/nivolumab combination, while high-disease-burden, fast-growing *BRAF*-mutated patients will likely receive a *BRAF* inhibitor in combination (e.g., vemurafenib [Zelboraf, Roche]), before ultimately moving on to ipilimumab/nivolumab when resistance develops.

The harder treatment decision comes, Dr. Weber said, in the two-thirds of patients with more indolent disease. Currently they are likely to receive a single-agent PD-1 inhibitor when

treated by community-based oncology practitioners. But the clinical trials assessing up-front combinations of a PD-1 inhibitor with an agent that suppresses Tregs and MDSCs may present other options.

Dr. Weber noted that among the most promising and potent agents in development is OX40 (AstraZeneca), a costimulatory



**Jeffrey S. Weber, MD, PhD**

receptor that potentiates T-cell receptor signaling on the surface of T lymphocytes. It is activated by specifically recognized antigens. Curtis et al.<sup>20</sup> observed that “OX40 engagement by ligands present on dendritic cells dramatically increases the proliferation, effector function, and survival of T cells.” They showed in a phase 1 study that one course of an anti-OX40 monoclonal antibody induced regression of at least one metastatic lesion in 12 of 30 patients.

Dr. Weber added that pembrolizumab with peginterferon is “actually looking quite promising” and that his phase 1b trial of peginterferon with ipilimumab had an excellent response rate among patients with unresectable melanoma.<sup>21</sup>

“So *old* interferon may actually increase the influx of T cells into the tumor and in some cases convert a *cold* tumor into a *hot* tumor—which makes it more susceptible to immunotherapy,” he explained. That ability makes interferon a potential partner for checkpoint inhibition. But as adjuvant therapy, Dr. Weber commented, “it will fade out—I don’t see a big role.”



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## Safety and Tolerability Issues

The PFS benefits of combining one of the newer PD-1 agents with ipilimumab come with a price in toxicity beyond the comfort level of some clinicians, Dr. Weber underscored. “It is significantly more toxic, and dealing with the side effects is a lot of work for the physicians, although the right training and some level of experience managing them can make a difference. It’s worth exposing the patients to the side effects if there is a major augmentation in survival—but we don’t know that yet.”

Many clinical trials are evaluating PD-1 inhibitors in combination with one or more agents, Dr. Weber said. “If any of these combinations can be shown to be less toxic and anywhere near as effective as nivolumab plus ipilimumab, ipilimumab plus nivolumab will go the way of the dodo,” he said. “Maybe everyone will use OX40 plus nivolumab. We’ll see if it’s well tolerated; maybe even nivolumab plus OX40 plus ipilimumab.”

If a clinical trial of PD-1/PD-L1 inhibition plus the indoleamine 2,3-dioxygenase inhibitor epacadostat (Incyte Corporation) demonstrates a 50% response rate with median survival in the 35 to 40 month range, Dr. Weber speculated, people will lose interest in combinations with ipilimumab. “But until then, that is the combination to beat.”

Preliminary results of a phase 1/2 study of epacadostat in combination with pembrolizumab, presented at the Society for the Immunotherapy of Cancer annual meeting in November 2015, may be a foreshadowing. In 54 patients with a variety of tumor types, the overall response rate was 53%, with only 2% of patients discontinuing the drug because of treatment-related adverse events.<sup>22</sup> Survival results will need another year or two to mature, Dr. Weber said. “This would be kind of nice, but right now the ipilimumab/nivolumab combination is a very effective regimen with long-term survival that’s very impressive.”

Finally, Dr. Weber pointed to the locally injected or intralesional therapies, such as talimogene laherparepvec (T-VEC), PV-10 (Rose Bengal 10% disodium, Provectus), and coxsackievirus A21 (Cavatak, Viralytics). Not only do they generally share the virtue of being devoid of dose-limiting toxicities, but they also may be able to “prime” the immune response, Dr. Weber said, so that “beyond trying to diminish the Treg and MDSC activity, you could augment T-cell activity, causing an influx of them to the tumor and making a cold tumor hot” (Figure 1).

Merrick Ross, MD, Professor of Surgery at MD Anderson Cancer Center in Houston, Texas, has suggested that the programmed cell death induced by the PD-1/PD-L1 agents may not cause the tumor to express antigens in a manner that evokes an immune

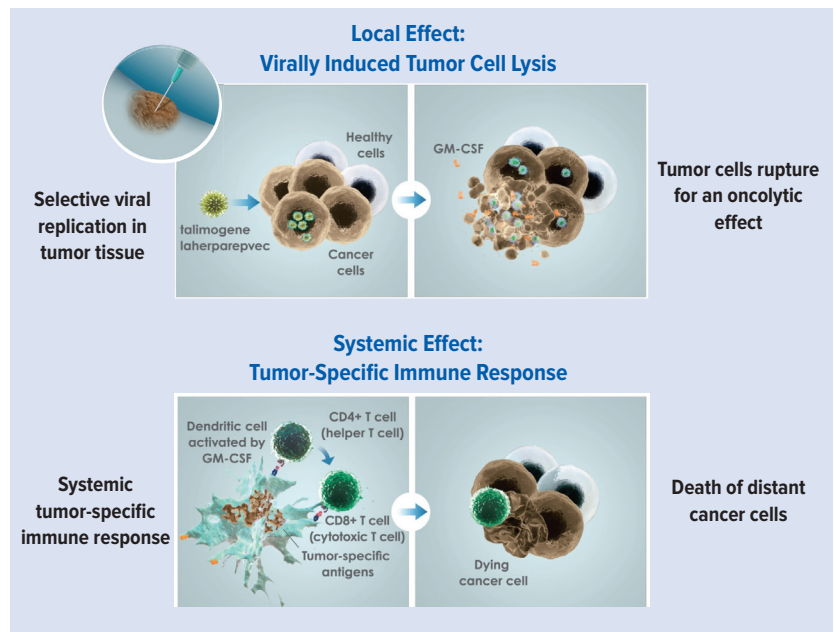
response.<sup>24</sup> On the other hand, viral vectors and a chemoablative agent like PV-10 actually rupture the tumor, releasing and presenting intact antigens. Such an effect, he said, could be synergistic with ipilimumab or other targeted immunotherapies, because it occurs at a different place in the immune system.

## The Role of Intralesional Injections

In October 2015, in the midst of the avalanche of checkpoint inhibitor approvals, T-VEC (Imlytic, Amgen), an oncolytic virus therapy derived from herpes simplex virus-1, received FDA approval for the treatment of melanoma lesions in the skin and lymph nodes. T-VEC, injected directly into melanoma lesions, replicates within tumor cells, causing them to rupture. In a multicenter study among 436 patients with unresectable metastatic melanoma, tumor size reductions lasting at least six months occurred in 16.3% of patients versus 2.1% of controls.<sup>25</sup>

Research into potential mechanisms of action for “bystander” effects—observed reductions in local or distant tumors that have not received intralesional injections—has suggested that antigenic fragments of ruptured tumors may stimulate a tumor-specific improvement in T-cell responses. Research with PV-10,<sup>26,27</sup> for example, has indicated that immune responses are tumor specific and associated with increases in CD8+ T cells in both animal and human research. In a phase 2 trial of PV-10 in 80 patients with metastatic melanoma, partial and complete

**Figure 1 Talimogene Laherparepvec: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects<sup>23</sup>**



The postulated dual mechanism of action of talimogene laherparepvec comprises two parts:

- A local oncolytic effect achieved by infection and selective replication of the virus in tumor tissue resulting in tumor cell lysis and local release of tumor antigens.
- Enhancement of a systemic antitumor immune response by expression of GM-CSF in the tumor microenvironment to recruit and activate antigen-presenting cells (e.g., dendritic cells). Dendritic cells have the capacity to capture antigens and induce proliferative responses and cytokine production in CD4+ and CD8+ T-lymphocytes to perpetuate immune responses against cancer cells.

GM-CSF = granulocyte-macrophage colony-stimulating factor; HSV-1 = herpes simplex virus-1

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responses were seen in 25% and 26% of patients, respectively, for a best overall response rate of 51%.<sup>28</sup> Among patients who had all lesions treated, the best overall response rate was 71% (50% complete responses, 21% partial responses). Uninjected nontarget lesion complete and partial responses occurred in 26% and 7%, respectively. There were no higher-grade treatment-related adverse events. An ongoing phase 3 trial comparing single-agent intralesional PV-10 versus systemic chemotherapy with dacarbazine or temozolomide is assessing treatment of locally advanced cutaneous melanoma. Included subjects are *BRAF* V600 wild-type and have failed or are not otherwise candidates for at least one immune checkpoint inhibitor. In addition, a phase 1b/2 trial of PV-10 with pembrolizumab in stage IV melanoma patients was initiated in September 2015.

A biomarker analysis from a phase 1b/2 trial of T-VEC plus ipilimumab versus T-VEC alone found increases from baseline after treatment with T-VEC and further after ipilimumab in total and activated CD8+ T cells in peripheral blood, plus increases in CD4 T cells expressing inducible T-cell costimulator. This indicates up-regulated CTLA-4 blockade following ipilimumab treatment. Patients with disease control after T-VEC had 1.4 times as many activated CD8 T cells.<sup>29</sup>

Although the FDA approval of T-VEC did not support the claim of distant effects, Robert Andtbacka, MD, Associate Professor at the University of Utah School of Medicine, said those effects were clearly evident in his clinical experience and have been reported with the other intralesional therapies. "They all have good effects in the injected lesions, also a regional response, and they also produce, to some extent, distant responses. They are all well tolerated and all potentially have the ability to modify the immune system so that when they are used in combination with other therapies they may improve responses."

Could an effect on distant disease, the ultimate cause of mortality in melanoma, be among the most important contributions of the intralesional therapies? "Current adjuvant therapies do not work as well as we would like them to," Dr. Andtbacka said. "So intralesional therapies in a neoadjuvant setting could reduce the risk of recurrence." In the phase 3 OPTiM trial, he said, the risk of developing new distant metastatic lung, liver, or visceral disease was reduced significantly (59%) among patients receiving T-VEC compared with granulocyte-macrophage colony-stimulating factor (GM-CSF). "This indicates to us that by giving T-VEC in these patients with regional disease, we may potentially reduce the risk of visceral disease." A multinational, phase 2 neoadjuvant study comparing T-VEC plus surgery to surgery alone is ongoing.<sup>30</sup>

### PD-1/PD-L1 in NSCLC

Dr. Herbst has been active in the research on both pembrolizumab and nivolumab. "Few patients with lung cancer are *not*

being considered for these drugs, both in the squamous and nonsquamous settings," he said. The medications are being administered in his own clinic at Yale, usually as second-line therapy in squamous lung carcinoma and as second- and third-line therapy in nonsquamous carcinoma.

Biomarker testing has been a particular focus of Dr. Herbst's research. "The data from the pembrolizumab trial suggests that using a biomarker can help you to identify patients who are more likely to benefit from the drug. With pembrolizumab it's the immunohistochemical (IHC) staining assay using the 22C3 antibody—the higher the expression, the more likely the patient is to respond and to survive longer," he said. In the recent KEYNOTE-010 trial,<sup>31</sup> in NSCLC patients in whom 50% or more of tumors were positive for PD-L1 (tumor proportion score), the HR for overall survival for pembrolizumab 2 mg/kg versus docetaxel was 0.54 (95% confidence interval, 0.38–0.77;  $P = 0.0002$ ). For the 10-mg/kg pembrolizumab group, the HR was 0.50 versus docetaxel (0.36–0.70;  $P < 0.0001$ ). Although it was of lesser magnitude, there was benefit, as

well, in those patients with lower levels of PD-L1.

The ability to use biomarkers to identify patients more likely to benefit from treatment is important because the checkpoint inhibitors, Dr. Herbst predicted, will be used in earlier, more curative settings among patients with previously untreated metastatic disease, as well as for maintenance or adjuvant therapy. But these agents really work in only about one-fourth of lung cancer patients, and knowing who should not be subjected to the potential side effects of, for example, a nivolumab/ipilimumab combination (in clinical testing) is clearly desirable. "While the combination does create more side effects, it does look like it is a little more active. You might be better off starting some with chemotherapy and reserving these agents for later on when there are no other options." Dr. Herbst added, "We still need more science about how the different agents and pathways interact to guide us toward the most rational combinations."

### Renal Cell Carcinoma

In renal cell carcinoma, "I think nivolumab will be used a great deal," said Mario Sznol, MD, Professor of Internal Medicine at Yale. "Although response rates are only in the 20% to 30% range in renal cell carcinoma studies, nivolumab does prolong overall survival and is very well tolerated in the vast majority of patients." While many clinicians will use nivolumab as second-line treatment after a vascular endothelial growth factor (VEGF) receptor inhibitor, Dr. Sznol's clinic tends to

treat renal cancer first with immunotherapy, despite the indication for second-line treatment, because in a small number of patients it can produce durable remissions—and possible cures. Dr. Sznol noted that the results are not as dramatic as those seen in melanoma, but for a number of patients the risk-benefit ratio is very favorable.



Robert Andtbacka, MD



Mario Sznol, MD



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A further and perhaps more fundamental question, according to Dr. Sznol, pertains to the order in which agents are given: Should interleukin-2 (IL-2) be offered first or nivolumab? And should they be given in combination in the future? Many patients would prefer nivolumab first because, unlike IL-2, it is an outpatient drug with very little toxicity. “We try nivolumab first, and in the subset who can tolerate IL-2 we may offer it subsequently as a part of standard of care. If those don’t work, we offer VEGF receptor inhibitors,” Dr. Sznol said.

Nivolumab’s approved indication in renal cell carcinoma is for use after progression on an angiogenic agent (e.g., VEGF inhibitors) such as sunitinib or pazopanib. Clinicians have learned to manage their side effects so that patients can tolerate them fairly well. The relative drawback of the VEGF inhibitors, Dr. Sznol observed, is that they tend not to produce cures or long-term remissions, and they require continued therapy. “Our goal is to cure people first—if there’s a small chance of doing that with immune therapies, we use those therapies first,” he said.

In addition, ipilimumab has demonstrated limited benefit (a 5% to 10% response) as monotherapy, but in combination with nivolumab in a phase 2 study<sup>32</sup> it was very promising, with 40% to 45% overall response rates, Dr. Sznol said. A phase 3 trial comparing nivolumab plus ipilimumab to sunitinib (Sutent, Pfizer) in patients with previously untreated advanced renal cell carcinoma has completed accrual. Sunitinib is an oral, small-molecule, multitargeted receptor tyrosine kinase inhibitor that includes VEGF receptors among its targets. In that trial, Dr. Sznol speculated, the sunitinib arm may show an early advantage in PFS, but later landmark analyses will likely show the combination arm to be better. The VEGF inhibitor, he explained, may be better at slowing disease progression in more patients, but then nivolumab/ipilimumab will likely produce more durable remissions.

Another combination of potential importance would partner VEGF inhibition with anti-PD-1 or anti-PD-L1 therapies. Atezolizumab (Roche’s investigational anti-PD-L1 agent) in combination with bevacizumab (Avastin, Roche) is being tested, as is nivolumab with pazopanib (Votrient, GlaxoSmithKline), and nivolumab or pembrolizumab with other VEGF receptor inhibitors. “In the future, we expect combinations will dominate treatment strategies, probably starting with combinations of immune therapies, followed by, if ineffective, immune therapies with VEGF receptor inhibitors,” Dr. Sznol concluded.

Dr. Herbst offered an overall impression of the giant steps witnessed in the recent immunotherapy approvals, particularly the checkpoint inhibitors: “It has been a revolution.”

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